SORSBY dystrophy
with c.113C>G, p.(Ser38Cys) mutation in exon 1 of *TIMP3*

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Synonyms : Sorsby pseudo-inflammatory macular dystrophy, haemorrhagic macular dystrophy, , Sorsby fundus dystrophy, Generalized fundus dystrophy, hereditary haemorrhagic chorioretinopathy, *TIMP3* exon 1 c.113C>G (p.S38C), founder mutation.

Arnold SORSBY (1900_1980)

First described in 1949 (1), Sorsby fundus dystrophy (SFD) is a retinal dystrophy who may acutely become manifest at the age of 40-50 years as a unilateral haemorrhagic and exudative maculopathy, which will also soon affect the second eye and, without treatment, will progress towards a disciform scar. This rapid onset could suggest an acute inflammatory disease however this is a neovascular response of a progressive chorioretinal disease. The first signs are macular drusen or yellow subretinal flecks. In some cases a progressive atrophy of the RPE and inner choroid is observed thickening and even sometimes ruptures of Bruch's membrane. The heredity of Sorsby fundus dystrophy is autosomal dominant. It is due to heterozygotic mutations of the *TIMP3* on 22q12. The mutations usually affect exon 5. In this paper we describe the clinical characteristics in a family where the mutation was found on exon 1 at c.113C>G p.(Ser38Cys)

The family described here is one of the three families with Sorsby fundus dystrophy followed at the University of Lille (France). The family is being followed for more than 50 years and has already been published (2-3). The family tree and the clinical characteristics are summarized in Tables 1 and 2. In this family the mutation is situated in exon 1 of the *TIMP3* gene and the change c.113C>G results in the modification Ser38Cys at the N terminal domain of TIMP3 protein (3-4-5-6).

Clinical aspects.

The patients remain asymptomatic up to the third or fourth decade. The fundus is usually normal although small white macular dots may be seen even as early as 50 years of age. The first symptoms are usually discrete: problems with prolonged dark adaptation, metamorphopsia and mild acquired blue-yellow dyschromatopsia.

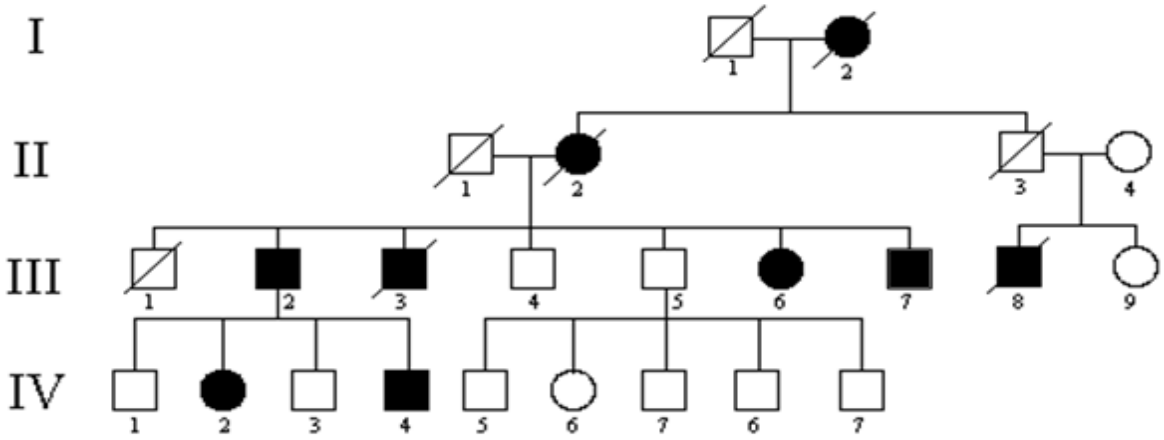

Table 1 : Family tree with mutation at c.113C>G (p.S38C) in exon 1 of *TIMP3*.

The disease becomes manifest between the ages of 40 and 55 years. The onset may be sudden due to subretinal newvessels or more progressive in case of chorioretinal atrophy that gradually affects the whole posterior pole (7). The median age for the neovascularisation in the first eye is 46 years and for the second eye 50 years (8). Dark adaptation problems are then present in 50 % of the cases.

Sex	Age at 1st examination	Age of first symptomss	Ophthalmoscopy	DA problems	Subretinal new vessels	Refraction	Last VA
II2 F	52	50	Drusen-like and extensive chorioretinal atrophy	+	yes	OD -7,00 (4,00)0° OS -2,00(-2,00)0°	FC
III2 M	52	50	Drusen-like and extensive chorioretinal atrophy	++	no	Discrete myopia OU	FC
III3 M	53	50	Drusen-like and extensive chorioretinal atrophy	++	yes	OD -3,25(-3,75)0° OS -3,25(-4,00)5°	FC
III6 F	49	49	Drusen-like, and extensive chorioretinal atrophy	++	no	OD -5,00 OS -5,00(-3,75)0°	FC

Table 2: Clinical characteristics. F: Female, M.: Male, OD: right eye, OS: left eye, OU both eyes, DA: dark adaptation, FC: finger counting

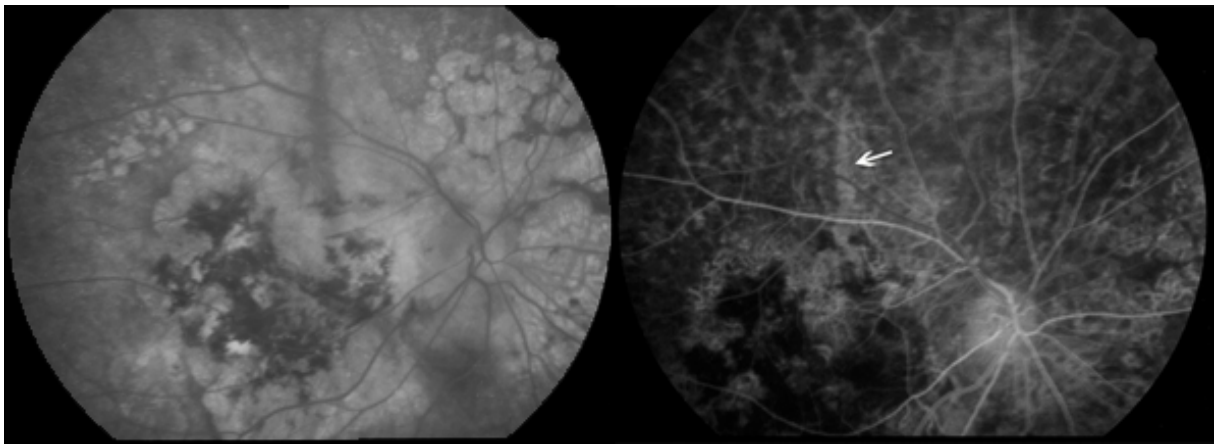

Figure: 1. Patient III3 aged 54 years. Pigmentary proliferation and scar formation following subretinal new vessels Possible rupture of Bruch's membrane (arrow) (9). The retinal blood vessels have a normal caliber.

The sudden loss of vision is related to the development of subretinal new vessels. Without treatment the lesion will progress to scar formation (Fig. 1).

Figure 2: Patient III2 at the age of de 53 years. Whereas the right fundus already presents RPE depigmentation, the left eye only shows discrete lesions

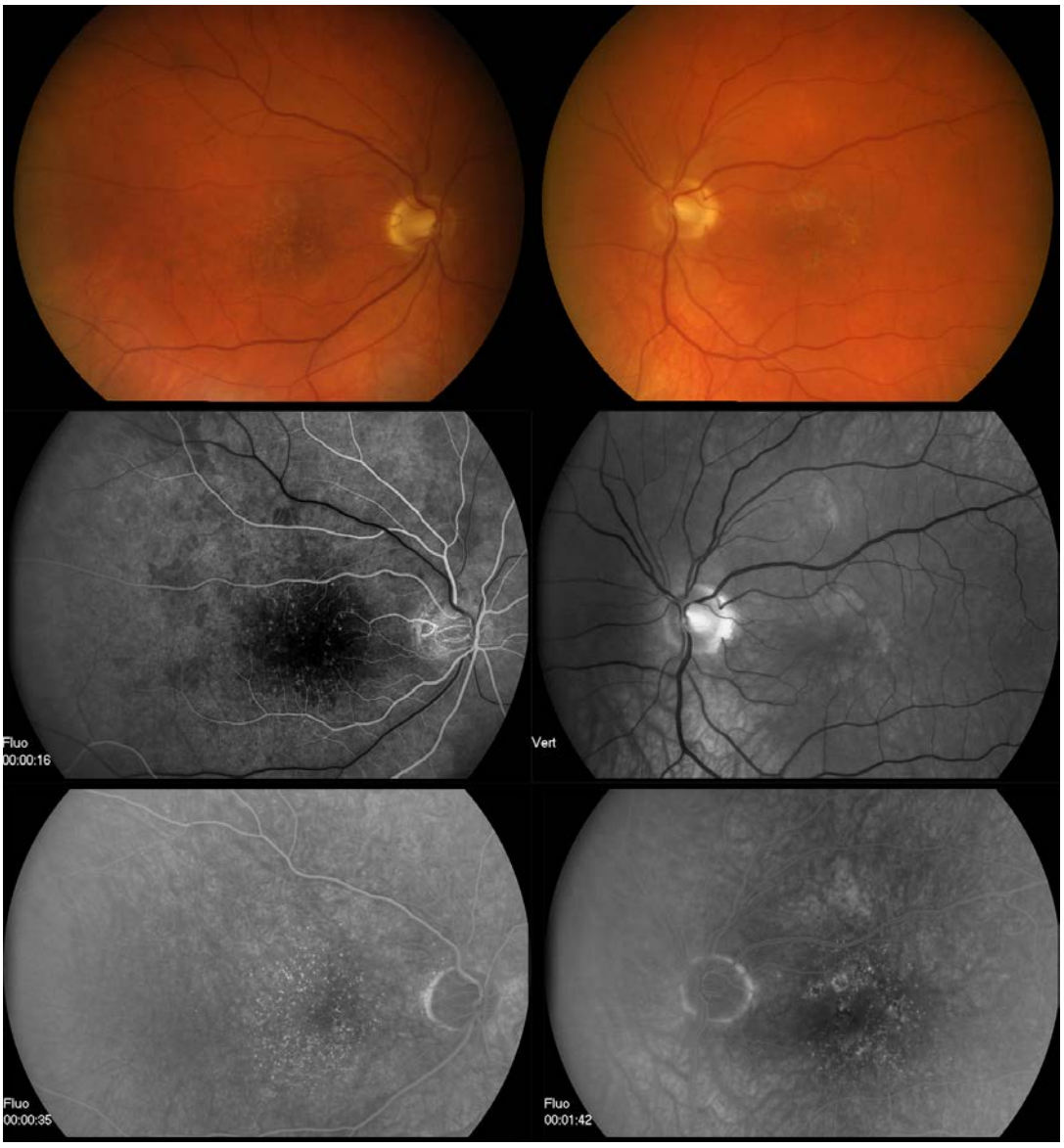

Figure: 3. Patient III7 aged 48 years. Small white macular dots may be seen even as early as 50 years of age.

If there are no subretinal new vessels macular atrophy will become apparent. The mean age is 50 years for the first eye and 52 for the fellow eye. The macular region becomes depigmented and the choroidal vessels become visible. This is associated with drusen like lesions (Fig. 2, 3, 4 and 5). They present as fine dots in the midperiphery and in the periphery. They are hardly visible on ophthalmoscopy, but become obvious on fluorescein angiography (Fig. 4). These lesions are associated to more or less confluent yellow flecks situated under the retinal vessels in the midperiphery sometimes mistakenly considered as deep exudates (fig. 3, 4). Whereas the posterior pole becomes depigmented, areas of atrophy of RPE and choriocapillaris appear in the periphery; they are accompanied by the drusenoïd punctiform lesions already (Fig. 6, 7).

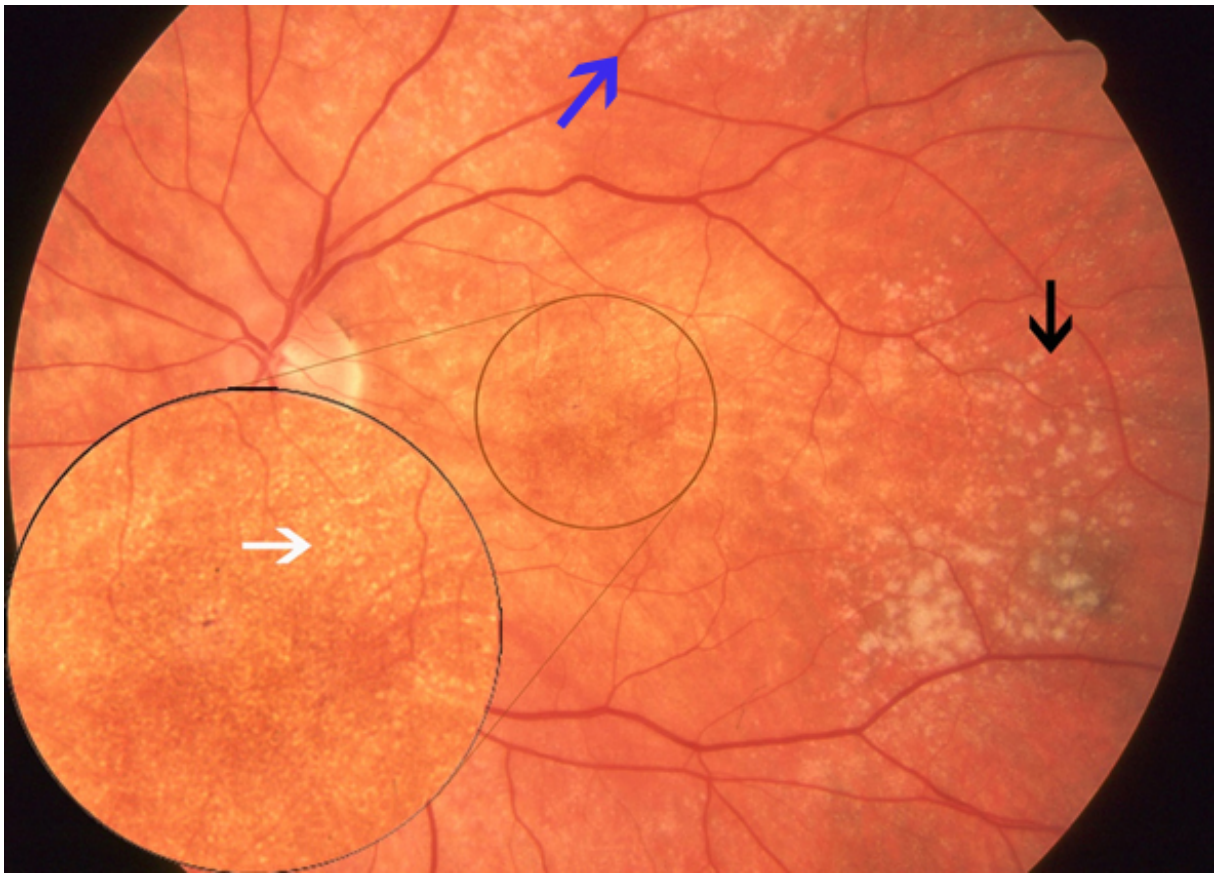

Figure 4: Patient III2 aged 53 years complaining of progressive loss of vision since 5 years. VA 5/10 RE and 6/10 LE. Increased transparency of the macula; the underlying choroidal vessels are visible. White arrow: macular microdrusen. Black and blue arrows; subretinal yellow flecks.

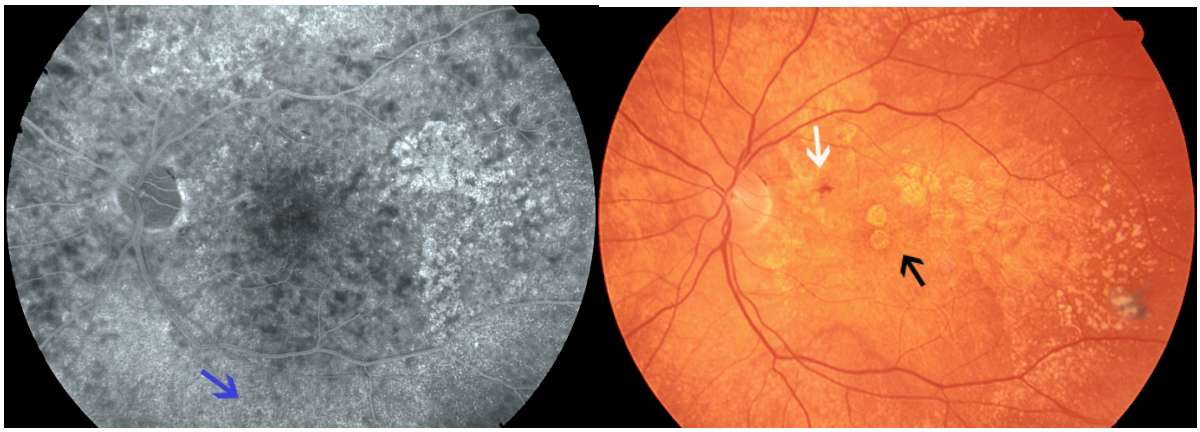

Figure 5: Patient III2 one year later. Fluorescein angiography highlights the depigmentation of the posterior pole. The micro drusen are hyperfluorescent (blue arrow). The yellow flecks are hypofluorescent. Increased lesions, macular atrophy becomes evident (black arrow), small haemorrhage near the optic disc (white arrow).

Figure 6.Progression of the lesions in patient III2. Areas of chorioretinal atrophy gradually progressing towards the periphery.

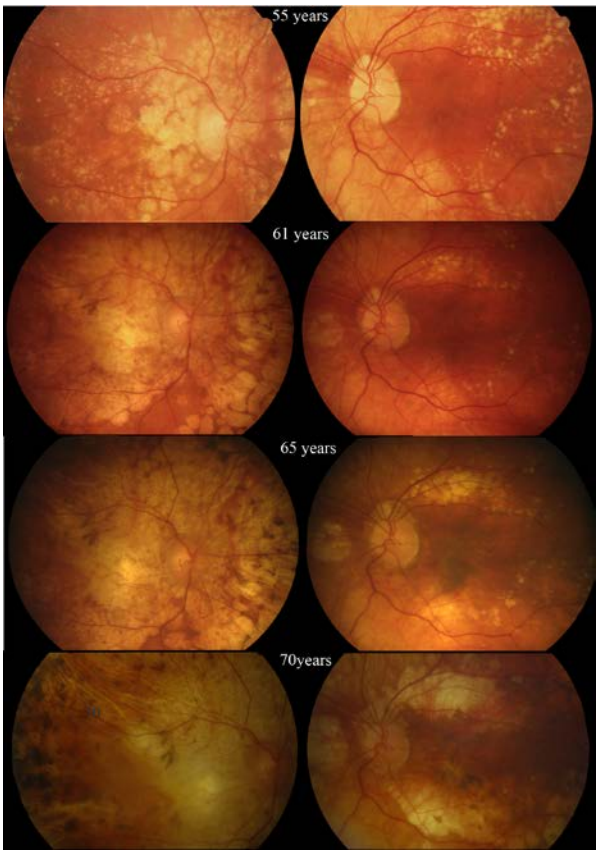

Figure 7 : Progression of the lesions in lpatient III6.

Between the ages of 45-55 years if the patient has not developed subretinal new vessels, areas atrophy of the RPE are seen similar to the ones in mid periphery. These areas may coalesce and cover the whole posterior pole within a few years. The risk of subretinal new vessels is still present (9)

The end stage is usually reached at the age of 60 years, sometimes earlier however. There is generalized chorioretinal atrophy and pigmented disciform scar. On OCT hyperreflective lesions are seen at the level of the RPE. Sometimes ruptures of Bruch's membrane are noticed.

Fluorescein angiography. In the early stages of the disease filling delay can be observed in some parts of the choriocapillaris, which gradually is altered and regresses with time in a centrifugal fashion from the posterior pole towards the fundus periphery (10). Fluorescein angiography also helps to localize leaking areas and choroidal neovascular membranes.

With **ICG angiography** an irregular hyperfluoresence of the veins is noted as well as vessel irregularities (narrowing and loops) and areas of vascular non perfusion (11) (Fig 8).

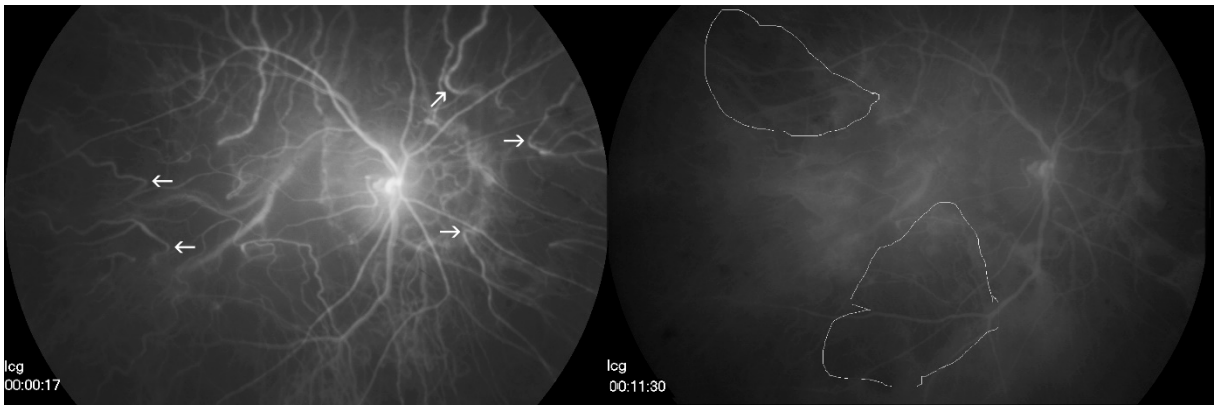

Figure 8: Patient III6 aged 63 years. ICG angiography shows choroidal vasular anomalies (arrows). On the late picture (right) the areas of choroidal non perfusion are outlined.

Auto fluorescence: Fundus autofluorescence is essentially normal in asymptomatic eyes. Later areas of hypofluorescence correspond to chorioretinal atrophy surrounded by a hyperfluorescent border suggestive of extension of atrophy or of CNV (Fig. 9). In the late stages with extensive chorioretinal atrophy the posterior pole becomes totally hypofluorescent.

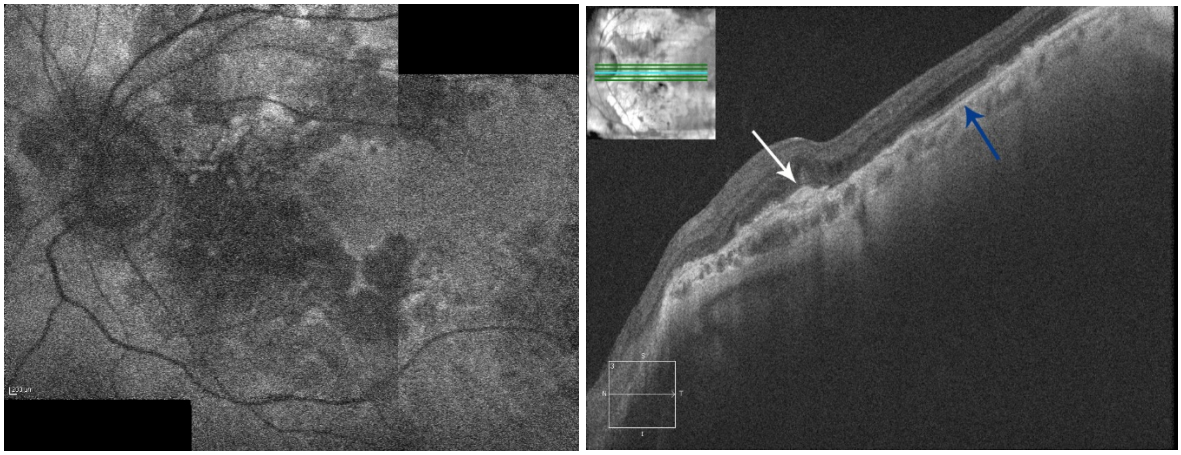

Figure 9: Patient III6. Hypofluorescence with hyperfluorescent borders on fundus autofluorescence and on OCT hyperreflective material under the fovea (white arrow), hyperreflective RPE-choroidal complex (blue arrow). Disappearance of the choriocapillaris and early atrophy of the large choroidal vessels

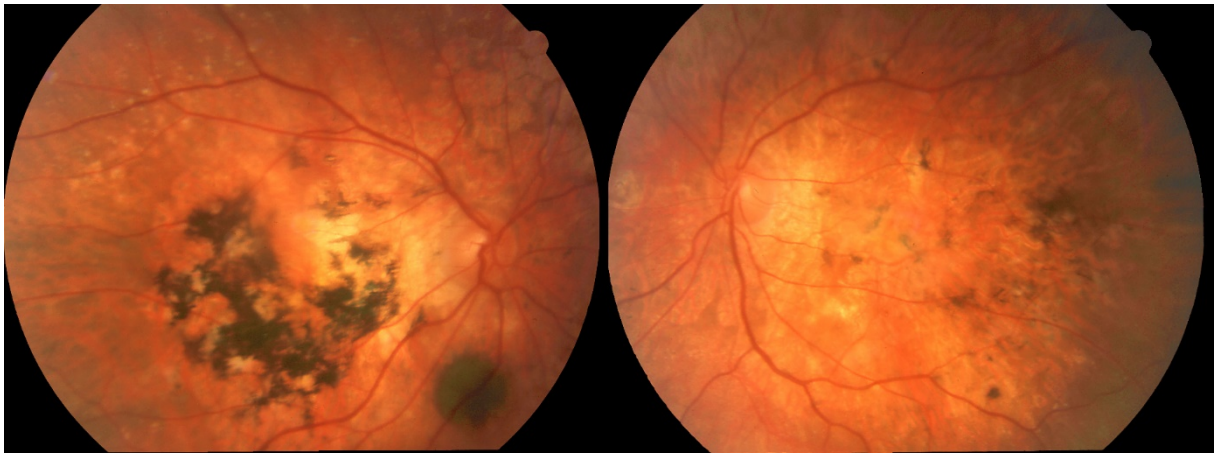

Figure 10 : Patient III3. Age of onset at 40 years old. The neovascular complication is unilateral at 54 ans.

Optical coherence tomography is useful for the detection of CNV and of intraretinal and subretinal fluid. Some areas present hyperreflectivity .

Electroretinography and dark adaptation. The full field ERG is initially normal but then the scotopic and later the photopic ERG will be affected. The dark adaptation is affected in an early stage with a raised scotopic threshold and later also of the photopic response. Vitamin A at 50.000 IU/d could possibly improve scotopic responses (12).

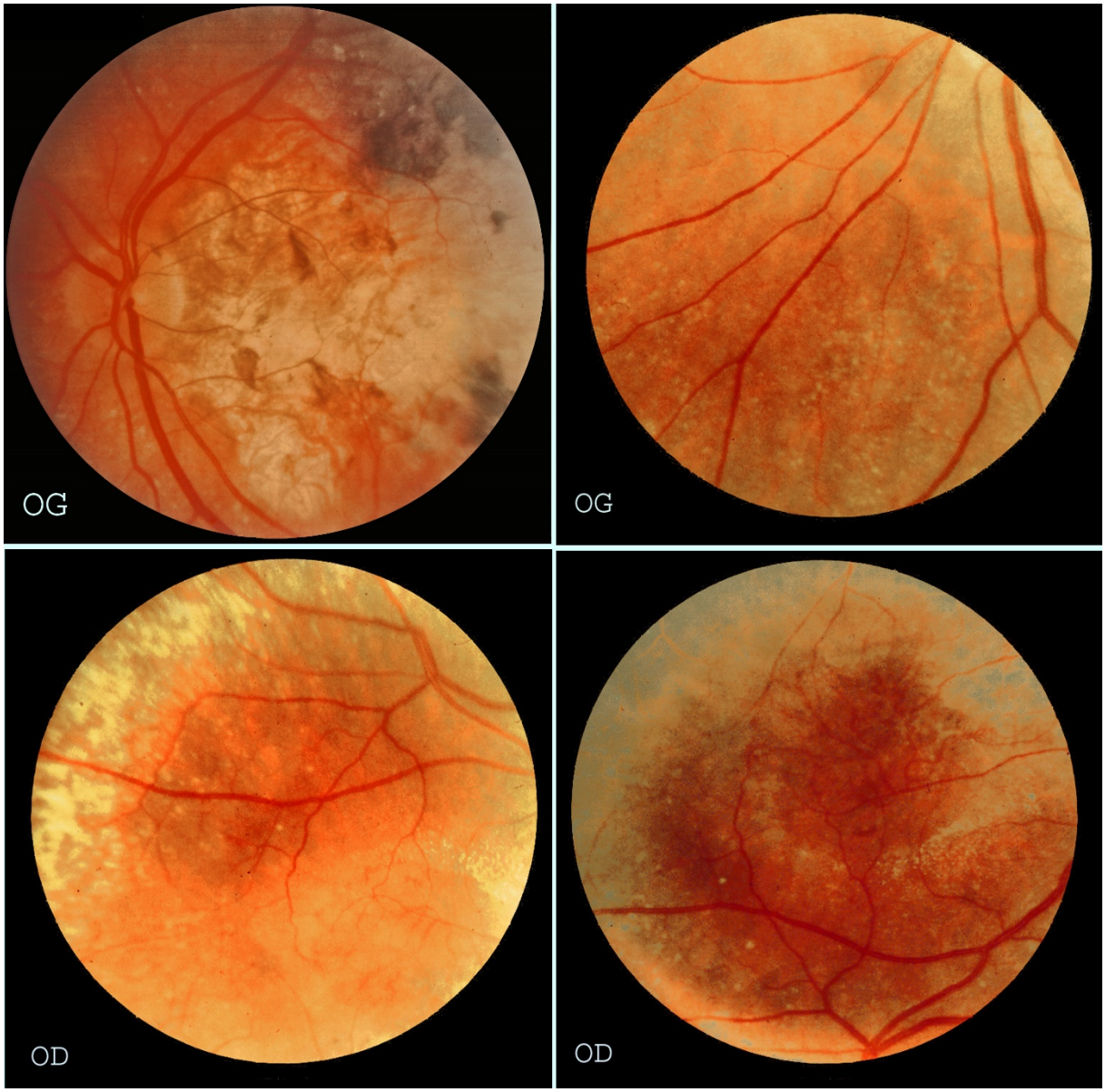

Figure 11 : Patient II2 in 1959 at the age of 52 years.

Clinical forms. The severity of Sorsby retinal dystrophy may be variable with the first signs appearing early or later in life. Some patients never present an acute exudative reaction. This variability could possibly be explained by the interference of other aging phenomena that may precipitate the formation of CNV (Fig 10, 11).

Systemic associations. In our family as well as in another family patients present pulmonary obstructive disease (3). The *TIMP3* gene is expressed in various tissues and its role in pulmonary obstruction has been demonstrated (3). Although this association has not yet been mentionned, this could indicate that SFD is a syndromic disease.

Molecular genetics. SFD is due to mutations in the *TIMP3* gene (tissue inhibitor metalloprotease 3) affecting most commonly exon 5 with the substitution of a cystein residue. Up to today, 18 mutations causing SFD have been identified (14). In our family, with an apparently less severe phenotype which becomes manifest at a later age not exon 5 but exon 1 is affected. *TIMP3* is expressed in the RPE. The coded protein regulates the activity of the metalloproteinase enzymes that play a role in the metabolism of Bruch's membrane. With inverse zymography it has been shown that the mutated protein keeps its inhibitory function (15, 16). In mice the modification of *TIMP3* provokes an accumulation of the mutated protein as dimers in the extracellular matrix. The retinal pigment epithelium loses its capacity to inhibit angiogenesis (interaction with fibulin containing epithelial growth factor) and becomes more susceptible to apoptosis (17). Another pathogenic mechanism is proposed for the mutation of TIMP3 in exon 1, p (Ser38Cys). The dimerization of mutant TIMP3 protein. It involve an intramolecular disulfide bonding with a break in TIMP3 molecule and established Cys36-Cys143 disulfide bond and formation of a novel Cys36-Cys38 that would eventually be associated with increase glycosylation of the protein TIMP3 (6).
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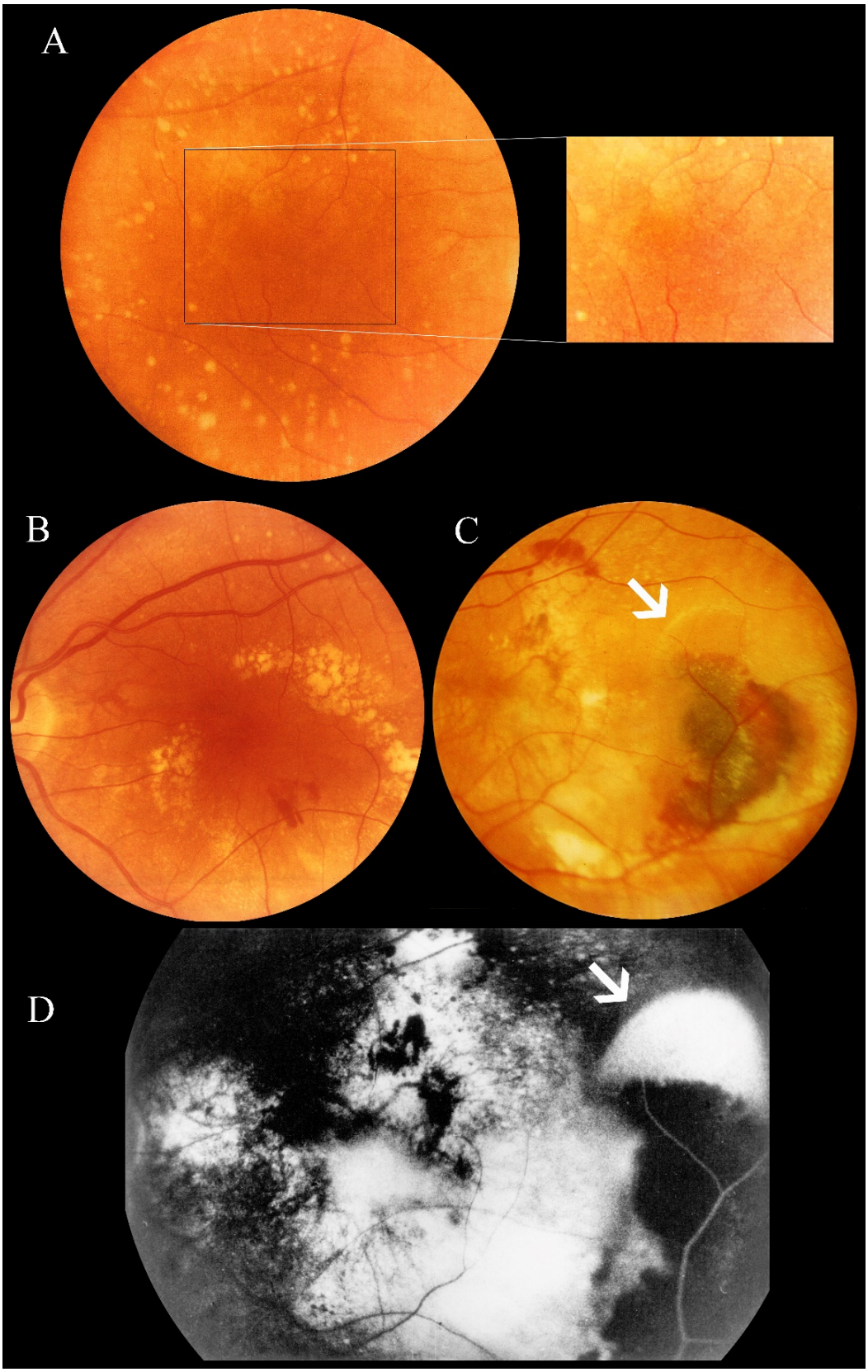

Figure 12: Massive subretinal neovascular response in another family (13). In A, atrophic areas and hardly visible macular microdrusen. B. Sister of the patient in A with a circinate retinopathy associated with some retinal haemorrhages. C and D rapid progression despite an early laser treatment towards an extensive serohaemorrhagic RPE detachment (arrow).

Differential diagnosis:

Ages Related Macular Degeneration (ARMD)). Drusen, neovascular complications and chorioretinal atrophy are features both of SFD and AMD. The age of onset is earlier and the neovascular response is more severe in SFD. Molecular genetics allows a correct diagnosis

Malattia leventinese (dominant drusen). This dystrophy due to mutation in the *EFEMP 1* gene, affects also Bruch's membrane. The depots are denser and diffuse, easily detectable with OCT. The molecular diagnosis is not always relevant due to genetic heterogeneity.

Late-Onset Retinal Dystrophy (L-ORD) The first symptoms of this rare dominantly inherited dystrophy appear in the fifth or sixth decade. Patients complain of night blindness and present drusen-like deposits. The disease progresses to central and peripheral degeneration with subretinal newvessels and chorioretinal atrophy.

Crinckled retinal Pigment Epitheliopathy of the Martinique. This disease is also dominantly inherited and affects Bruch's membrane. This disease has some striking similarities with SFD and one of the patients of the original publication was erroneously diagnosed as SFD. Molecular testing however excluded this diagnosis (18).

Treatment: Vitamin A (50 000 units per day) was proposed as treatment for the problems of dark adaptation. The CNV was initially treated with argon laser, photodynamic therapy or intravitreal steroids with limited success. These treatments have been abandoned and have been replaced by anti-VEGF injections (5-6).

Conclusion: In the family described here the *TIMP3* gene mutation is situated on exon 1 1 c.113C>G (p.S38C) but the chorioretinal manifestations are similar to the ones observed in patients with mutation in exon 5. The main difference is the appearance at a somewhat later age and the preferential evolution towards atrophy. However in 2 of our 5 patients polypoidal choroidal vasculopathy was found in both eyes.

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